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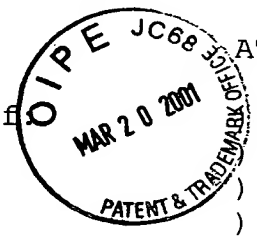
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



ATTY.'S DOCKET: REIMANN=1

In re Application of)
Jorg REIMANN et al) Examiner: A. Beckerleg
Appln. No.: 09/241,595) Art Unit: 1632
Confirmation No.: 8928) Washington, D.C.
Filed: February 2, 1999) March 20, 2001
For: DELIVERY OF IMMUNOGENIC MOLECULES VIA HbsAg PARTICLES)

RESPONSE

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action of September 20, 2000, a petition and a payment for a three month extension of time are attached hereto and applicants' comments follow below.

The Office Action has been carefully reviewed. No claims are allowed. Claims 1-30 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Briefly, the present invention is based on the finding that HBsAg particles containing an antigenic molecule (claim 1) and optionally an immunostimulating molecule (claim

8) that may modulate or stimulate a CTL response, which in the absence of these molecules, would not have been modulated or stimulated. It is shown in the present application that priming of a CTL response is independent from other immune response mechanisms, such as antibody production. Thus, administration of the composition of the present invention may result in a CTL response, without antibodies or at least not a significant level of antibodies produced.

Claims 1-5, 7-8, 10-13, 16-17, 20-21, 23, and 25-30 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner states that the specification does not provide a written description for any molecules which are not proteins. The specification is said to disclose immunostimulatory proteins such as cytokines or bacterial toxins and antigenic proteins or peptides such as the HIVenv/V3 peptide. However, the examiner asserts that it lacks guidance concerning the identity and chemical composition of antigenic molecules other than those composed of amino acids. In regards to the recitation of immunostimulatory oligonucleotides, the examiner indicates that the specification does not describe

whether the oligonucleotides comprise non-coding or protein coding sequence, or in the case of coding sequence, what the oligonucleotides encode.

In the absence of any description of genes or nucleic acids encoding any immunostimulatory oligonucleotide or non-coding nucleic acid sequences which are immunostimulatory, the examiner takes the position that the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides which may be immunostimulatory, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description is said to require more than a mere statement that it is part of the invention; the nucleic acid itself is required. Therefore, the examiner concludes that the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for biologically active molecules which are not proteins. This rejection is respectfully traversed.

At the time of filing the present application, oligonucleotides (ODNs) as adjuvants for stimulating an immune response were well characterized in man and mouse and were widely used in experimental vaccination protocols. Thus, a person versed in the art would have known to identify and select ODNs for use in the method of the present invention.

Furthermore, ODNs can be successfully loaded into HBsAg particles. Recently, it was also shown that such particles containing ODNs produced a greater CTL response than ODNs alone (Reimann J. et al, International Immunology 11(7):1093-1102, a copy of which will be provided in a Supplemental Response). The biochemical properties of ODNs, including their loading into the HBsAg particles should be similar, as they are all comprised of nucleic acids that have a similar charge and size as would be understood by those of skill in the art. What is important is that the ODNs contain an immunostimulating consensus motif which is well defined in mouse, man and other species and accordingly is well known to those versed in the art.

Claims 1-30 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is more nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

I. The examiner asserted that the present invention does not provide an enabling disclosure for making HBsAg particles which non-covalently contain inside the particles any biologically active protein. Further, the examiner asserted that the methodology described in the specification for

encapsulating the biologically active proteins is effective only for soluble proteins and would not work for insoluble/hydrophobic molecules.

HBsAg particles have been in the art for the last 20 years. They have been and still are extensively used for vaccination against HBV. The particles used in the present invention are well characterized and the present invention clearly describes the manner in which the immunogenic and immunostimulating molecules are non-covalently incorporated into the particles, e.g., by incubating the particles in an aqueous medium in the presence of the molecule (see page 3, lines 19-31).

Further on page 3, incorporation of glycolipid into the exterior surface of the particles is described, i.e., by co-incubating the glycolipids with the particles in the presence of the biologically active compound (e.g., a transfer protein). Thus, it is in fact not correct that the specification is only enabling for hydrophilic molecules. The specification clearly indicates that hydrophobic molecules, such as glycolipids, may be incorporated into the exterior of the particles with the assistance of a biologically active compound (page 3, lines 32-34).

The definition of the term "encapsulation" provided on page 6, lines 16-23, of the specification discloses that the

biologically active molecules may be "encapsulated within the interior of an HBsAg particle" through the pores within the particle's surface, or be "exposed or present at the surface of the particle". Thus, applicants believe that those skilled in the art would understand that hydrophobic proteins or peptides or other hydrophobic molecules are preferably incorporated into the exterior of the particles as with glycolipids and that they do not necessarily penetrate into the interior of the particle. The examiner's reference to US Patent No. 5,039,522 only strengthens the fact that the invention may work also for hydrophobic molecules. This reference cited by the examiner describes the absorbance of a peptide with a hydrophobic tail to the surface of HBsAg particles. The present invention also claims the incorporation of naturally occurring hydrophobic molecules and makes the first use of such compositions for modulating/stimulating the immune response.

II. The examiner asserted that there are several factors which significantly affect the generation of immune responses to an antigen, including genetics, doses or concentration of an antigen and route of its administration and that the specification does not provide sufficient guidance for generating any kind of immune response, using any antigen, any cytokine or bacterial toxin and any dosage and route of administration.

While applicants agree that with particular antigens and cytokine combinations, certain routes and dosage schedules will provide better results than others, it should be well recognized by those skilled in the art how to determine the specific route and dosage for each formulation, particularly in view of the fact that HBsAg particles are well characterized. In fact, at the time the present application was filed, there were several publications dealing with different aspects of HBsAg delivery to animals as well as humans. Such publications show that HBsAg particles may be delivered through various routes. For example, one publication shows that these particles may be administered by injection, including intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous injection (Reimann J. et al., Vaccine 16:949-954 (1998) a copy of which will be provided in a Supplemental Response to the examiner describing routes of administration of HBsAg-encoding plasmid DNA and recombinant HBsAg particles).

Other publications dealing with vaccination with HBsAg include, *inter alia*, (1) Ellis, R. W., New and improved vaccines against hepatitis B. I. Recombinant-derived vaccines against hepatitis B. In New Generation Vaccines, G. C. Woodrow and M. M. Levine, eds., Marcel Dekker, Inc., New York, pp. 439-447 (1990); and (2) Ellis, R. W. and P. J. Kniskern, Recombinant hepatitis B vaccines. In Molecular Biology of the

Hepatitis B Virus. A. McLachlan, ed., CRC Press, Boston, pp. 307-322 (1991). Copies of the relevant pages of these publications also will be provided in a Supplemental Response to the examiner.

Thus, contrary to the examiner's position, applicants believe that those versed in the art would have known and would have been enabled for how to make use of the method of the present invention.

III. The examiner asserted that the specification is not enabling with regards to stimulation of the immune responses.

The present invention shows that, depending on the immunogenic molecule loaded into the HBsAg particles (e.g., IL-12) CTL can be induced in certain so called 'non responder' mouse strains (i.e., which did not respond to the empty particles).

It is emphasized the experiments disclosed in the specification of the present invention deal with stimulation or modulation of an MHC-I restricted virus specific response of CD8 cytotoxic T lymphocytes (CTL) response. Thus, while priming a CTL response, other immune responses (e.g., antibodies production) may or may not be influenced. Therefore, referring to the examiner's position on page 6, middle paragraph, of the Office Action, it is not essential to

show antibody responses as long as a CTL response is stimulated or modulated.

With regard to the result shown in Fig. 6D with HBsAg particles encapsulating IL-2, applicants discovered afterwards that IL-2 became inactive under the loading conditions used in that particular experiment and therefore was unable to induce the desired CTL response. However, this certainly does not indicate that the specification is non-enabling. In the same experiment, under the same loading conditions used for IL-2, two other cytokine immunostimulating molecules, IL-12 and IFNγ, certainly demonstrated the stimulation of a CTL response. Applicants note that there is no requirement that all immunostimulating molecules within a recited genus be operative, just that the claims are enabling to one of skill in the art without undue experimentation. Certainly, IL-12 and IFNγ are enabled and it is submitted that IL-2 either is merely an inoperative species within the genus of immunostimulating molecules, which is not indicative of non-enablement, or can be made operative by optimizing result-effective parameters/variables, i.e., the loading conditions, without undue experimentation as would be well within the high skill level of those in the art.

IV. The examiner refers on pages 9-10 of the Office Action to immunization against HBV or HIV and asserts that

there is no data correlating between a CTL response and the success in immunization against HBV and HIV infection.

Applicants refer the examiner to the numerous publications teaching the correlation between CTL response ad immunization with HIV or HBV antigens, some of which are identified below:

HBV-related publications:

Maini, M. K. et al., Gastroenterology 117:1386-1396 (1999)

Bertoletti, A. And M. K. Maini Curr. Opin. Microbiol. 3:387-392 (2000)

Maini, M. K. et al., J. Exp. Med. 191:1296-1280 (2000)

HIV-related publications:

Carmichael, A. et al., J. Exp. Med. 177:249-256 (1993)

Hsueh, F. W. et al., Cell. Immunol. 159:271-279 (1994)

Kent, S. J. et al., J. Virol. 70:4941-4947 (1996)

Levy, J. A. et al., J. Infect. Dis. 177:470-472 (1998)

Jin, X. et al., J. Exp. Med. 189:991-998 (1999)

These publications show that it is possible to induce an immune response by the use of HBV or HIV antigens. Therefore, the application should be regarded as enabling for claims directed to a method of stimulating or modulating an immune response against HBV and HIV, as recited in the claims.

In this regards, it is respectfully pointed out to the examiner that, while it may be that the end target of this research to develop a vaccine against these diseases, it is well recognized that many additional experiments need to be conducted (pre-clinical and clinical experiments) before presenting a successful vaccine. Nonetheless, the present invention provides an efficient tool for inducing an effective immune response, which is evidently an important step towards obtaining such a vaccine. Consequently, as the claims are merely directed to a method and composition for stimulating or modulating an immune response, applicants submit that the specification is indeed enabling.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

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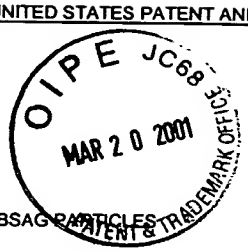

In Re Application of: REIMANN et al.

Application No.: 09/241,595

Filed: February 2, 1999

For: DELIVERY OF IMMUNOGENIC MOLECULES VIA HBSAG PARTICLES

Art Unit: 1632

Examiner: A Beckerleg

Washington, D.C.

Atty.'s Docket: REIMANN=1

Date: March 20, 2001

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THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith is a [ ] Amendment [X] RESPONSE in the above-identified application.

[XX] Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted

[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

[ ] No additional fee is required.

[XX] The fee has been calculated as shown below:

	(Col.) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID	(Col. 3) PRESENT EXTRA EQUALS
TOTAL	* 30	MINUS	** 30	0
INDEP.	* 4	MINUS	*** 4	0
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				

SMALL ENTITY RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDITIONAL FEE
x 9	$		x 18	$
x 40	$		x 80	$
+ 135	$		+ 270	$
ADDITIONAL FEE TOTAL	$	OR	TOTAL	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time

If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity			Other Than Small Entity		
Response Filed Within			Response Filed Within		
[ ] First	- $	55.00	[ ] First	- $	110.00
[ ] Second	- $	195.00	[ ] Second	- $	390.00
[XX] Third	- $	445.00	[ ] Third	- $	890.00
[ ] Fourth	- $	695.00	[ ] Fourth	- $	1390.00
Month After Time Period Set			Month After Time Period Set		

[ ] Less fees ($_____) already paid for ___ month(s) extension of time on _____.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] Credit Card Payment Form, PTO-2038, is attached, authorizing payment in the amount of $ 445.00.

[ ] A check in the amount of $_____ is attached (check no.).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

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